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 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  SEP 09   CA/CAplus records now contain indexing from 1907 to the
                   present
 NEWS  4  AUG 05   New pricing for EUROPATFULL and PCTFULL effective
                   August 1, 2003
 NEWS  5  AUG 13   Field Availability (/FA) field enhanced in BEILSTEIN
 NEWS  6  AUG 18   Data available for download as a PDF in RDISCLOSURE
 NEWS  7  AUG 18   Simultaneous left and right truncation added to PASCAL
 NEWS  8  AUG 18   FROSTI and KOSMET enhanced with Simultaneous Left and Righ
                   Truncation
 NEWS  9  AUG 18   Simultaneous left and right truncation added to ANABSTR
 NEWS 10  SEP 22   DIPPR file reloaded
 NEWS 11  SEP 25   INPADOC: Legal Status data to be reloaded
 NEWS 12  SEP 29   DISSABS now available on STN
 NEWS 13  OCT 10   PCTFULL: Two new display fields added
 NEWS 14  OCT 21   BIOSIS file reloaded and enhanced
 NEWS 15  OCT 28   BIOSIS file segment of TOXCENTER reloaded and enhanced
 NEWS 16  NOV 24   MSDS-CCOHS file reloaded

 NEWS EXPRESS  NOVEMBER 14 CURRENT WINDOWS VERSION IS V6.01c, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 23 SEPTEMBER 2003
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
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FILE 'HOME' ENTERED AT 15:56:23 ON 02 DEC 2003

=> file, medline, uspatful, dgene, fsta, wpids, hcaplus, embase
FILE, IS NOT A RECOGNIZED COMMAND
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For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).
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=> s articular cartilage
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command can only be used to look at the index in a file which has an
index.  Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of
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                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 1.26       1.26

FILE 'MEDLINE' ENTERED AT 15:59:39 ON 02 DEC 2003

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=> s BMP-12
L1          426 BMP-12

=> s BMP-2
L2         5758 BMP-2

=> s articular cartilage
L3        53365 ARTICULAR CARTILAGE

=> s l3 and regeneration
L4         2094 L3 AND REGENERATION

=> s osteochondral graft
L5          119 OSTEOCHONDRAL GRAFT

=> s l5 and l4
L6            9 L5 AND L4

=> d l6 ti abs ibib tot

L6   ANSWER 1 OF 9  USPATFULL on STN
TI     Tissue maintenance system that applies rhythmic pulses of pressure
AB     A growth support scaffold for cells and tissue is formed of naturally
       derived connective or skeletal tissue which has been treated for
       elimination of cellular and cytosolic elements, and modified by
       cross-linking with hyaluronic acid, proteoglycans, glycosaminoglycans,
       chondroitin sulfates, heparan sulfates, heparins or dextran sulfates.
```

The scaffold may contain cell adhesive molecules and growth factors, and can be formulated as a malleable prosthesis. A tissue maintenance system is provided containing a chamber having a constant atmosphere which may contain the scaffold impregnated with cells, a medium-containing reservoir, a pump which can be computer controlled for circulating the medium between the chamber and reservoir and may change direction of medium flow every 1 to 3 minutes, and a pressure generator, which can be the pump, for producing rhythmic pulses of pressure such as between 0.5 to 30 atm and frequency of 5-300 per minute.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2003:273353 USPATFULL		
TITLE:	Tissue maintenance system that applies rhythmic pulses of pressure		
INVENTOR(S):	Nevo, Zvi, Herzliya, ISRAEL Robinson, Dror, Shimson, ISRAEL		
PATENT ASSIGNEE(S):	Ramot at Tel Aviv University Ltd., Ramot Aviv, ISRAEL (non-U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6632651	B1	20031014
APPLICATION INFO.:	US 1999-345138		19990706 (9)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	GRANTED		
PRIMARY EXAMINER:	Naff, David M.		
LEGAL REPRESENTATIVE:	Ladas & Parry		
NUMBER OF CLAIMS:	10		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	11 Drawing Figure(s); 8 Drawing Page(s)		
LINE COUNT:	541		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 2 OF 9 USPATFULL on STN

TI Trabecular bone-derived human mesenchymal stem cells

AB The present invention discloses an in vitro engineered **osteochondral graft** comprising a porous matrix block, more particularly, a porous polylactic acid polymer block, press-coated with mesenchymal stem cells (MSCs), wherein a cartilage layer is formed on the surface of the matrix block. This invention may be used for treating **articular cartilage** defects.

ACCESSION NUMBER:	2003:72422 USPATFULL		
TITLE:	Trabecular bone-derived human mesenchymal stem cells		
INVENTOR(S):	Noth, Ulrich, Wurzburg, GERMANY, FEDERAL REPUBLIC OF Tuan, Rocky S., Chester Springs, PA, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003050709	A1	20030313
APPLICATION INFO.:	US 2002-82705	A1	20020225 (10)
	NUMBER		DATE
PRIORITY INFORMATION:	US 2001-270977P		20010223 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	David S. Resnick, NIXON PEABODY LLP, 101 Federal Street, Boston, MA, 02110		
NUMBER OF CLAIMS:	28		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	5 Drawing Page(s)		
LINE COUNT:	852		

L6 ANSWER 3 OF 9 USPATFULL on STN
TI Device for **regeneration** of **articular cartilage** and other tissue
AB An implantable device for facilitating the healing of voids in bone, cartilage and soft tissue is disclosed. A preferred embodiment includes a cartilage region comprising a polyelectrolytic complex joined with a subchondral bone region. The cartilage region, of this embodiment, enhances the environment for chondrocytes to grow **articular cartilage**; while the subchondral bone region enhances the environment for cells which migrate into that region's macrostructure and which differentiate into osteoblasts. A hydrophobic barrier exists between the regions, of this embodiment. In one embodiment, the polyelectrolytic complex transforms to hydrogel, following the implant procedure.

ACCESSION NUMBER: 2003:65819 USPATFULL
TITLE: Device for **regeneration** of **articular cartilage** and other tissue
INVENTOR(S): Brekke, John H., Duluth, MN, UNITED STATES
Bradica, Gino, Claremont, NH, UNITED STATES
Goldman, Scott M., Paoli, PA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003045943	A1	20030306
APPLICATION INFO.:	US 2002-199961	A1	20020719 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-206604, filed on 7 Dec 1998, GRANTED, Pat. No. US 6264701 Division of Ser. No. US 1994-242557, filed on 13 May 1994, GRANTED, Pat. No. US 5981825
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Alan D. Kamrath, Kensey Nash Corporation, 55 E. Uwchlan Avenue, Exton, PA, 19341
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
LINE COUNT: 1263

L6 ANSWER 4 OF 9 USPATFULL on STN
TI Device for **regeneration** of **articular cartilage** and other tissue
AB An implantable device for facilitating the healing of voids in bone, cartilage and soft tissue is disclosed. A preferred embodiment includes a cartilage region comprising a polyelectrolytic complex joined with a subchondral bone region. The cartilage region, of this embodiment, enhances the environment for chondrocytes to grow **articular cartilage**; while the subchondral bone region enhances the environment for cells which migrate into that region's macrostructure and which differentiate into osteoblasts. A hydrophobic barrier exists between said regions, of this embodiment. In one embodiment, the polyelectrolytic complex transforms to hydrogel, following the implant procedure.

ACCESSION NUMBER: 2002:55324 USPATFULL
TITLE: Device for **regeneration** of **articular cartilage** and other tissue
INVENTOR(S): Brekke, John H., Duluth, MN, UNITED STATES
Goldman, Scott M., Paoli, PA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002032488	A1	20020314
APPLICATION INFO.:	US 2001-909027	A1	20010719 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-206604, filed

on 7 Dec 1998, GRANTED, Pat. No. US 6264701 Division of Ser. No. US 1994-242557, filed on 13 May 1994, GRANTED, Pat. No. US 5981825

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Alan D. Kamrath, Kensey Nash Corporation, 55 E. Uwchlan Avenue, Exton, PA, 19341
NUMBER OF CLAIMS: 56
EXEMPLARY CLAIM: 1
LINE COUNT: 1349

L6 ANSWER 5 OF 9 USPATFULL on STN
TI Scaffold matrix and tissue maintaining systems
AB The invention concerns a scaffold which is used as a growth supportive base for various cells and tissue explants from three-dimensional tissue comprising naturally derived connective or skeletal tissue into attached flakes having a very high porosity. Alternatively the scaffold is composed of fused epiphyses.

ACCESSION NUMBER: 2002:16925 USPATFULL
TITLE: Scaffold matrix and tissue maintaining systems
INVENTOR(S): Nevo, Zvi, Herzliya, ISRAEL
Robinson, Dror, Shimshon, ISRAEL
PATENT ASSIGNEE(S): RAMOT UNIVERSITY AUTHORITY FOR APPLIED RESEARCH & INDUSTRIAL DEVELOPMENT LTD. (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002009805	A1	20020124
	US 6652872	B2	20031125
APPLICATION INFO.:	US 2001-826389	A1	20010404 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-345138, filed on 6 Jul 1999, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LADAS & PARRY, 26 WEST 61ST STREET, NEW YORK, NY, 10023
NUMBER OF CLAIMS: 32
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Page(s)
LINE COUNT: 903

L6 ANSWER 6 OF 9 USPATFULL on STN
TI Multi-stage collagen-based template or implant for use in the repair of cartilage lesions
AB The invention is a template to aid in the **regeneration** of **articular cartilage**. The template is formed by combining a porous collagen sponge ("collagen matrix") with a dense collagen membrane. The dense collagen membrane is placed on the surface of the cartilage defect to prevent cell migration from the subchondral plate and vasculature. The collagen membrane will allow movement and exchange of fluids, nutrients, cytokines and other factors necessary for cartilage **regeneration**. The collagen matrix has been developed to allow attachment and growth of cells, specifically chondrocytes which are normally found in **articular cartilage**. The collagen matrix can be combined with chondrocytes in vitro, and therefore serve to transport cultured cells to the defect site and to retain the cells in position following implantation. Procedures are described to effectively use the two-staged template, and to fix the template to the repair site.

ACCESSION NUMBER: 2000:80202 USPATFULL
TITLE: Multi-stage collagen-based template or implant for use in the repair of cartilage lesions
INVENTOR(S): Pachence, James M., Hopewell, NJ, United States

	Frenkel, Sally, Flushing, NY, United States Menche, David, New York, NY, United States
PATENT ASSIGNEE(S):	The Hospital for Joint Disease Orthopaedic Institute, New York, NY, United States (U.S. corporation)

NUMBER	KIND	DATE
PATENT INFORMATION:	US 6080194	20000627
APPLICATION INFO.:	US 1995-385290	19950210 (8)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Prebilic, Paul B.
LEGAL REPRESENTATIVE:	Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd.
NUMBER OF CLAIMS:	16
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	4 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT:	636

L6 ANSWER 7 OF 9 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN

TI Engineered osteochondral grafts for promoting growth of cartilage in patient at defect site in need of repair, comprises matrix block and first population of mesenchymal stem cells forming cartilage layer on top surface of a matrix block.

AN 2003-576306 [54] WPIDS

AB US2003050709 A UPAB: 20030821

NOVELTY - An engineered **osteochondral graft** for promoting the growth of cartilage in a patient at a defect site in need of repair, comprises a matrix block and a first population of mesenchymal stem cells, press-coated on a top surface of the matrix block, and forming a cartilage layer on the top surface of the matrix block, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method of fabricating an **osteochondral graft**, comprising contacting a top surface of a matrix block with a high-density pellet of a population of mesenchymal stem cells (MSCs) for a first period of time enough to form a cell-matrix structure, and culturing the cell-matrix structure in a chondrogenic differentiation medium for a second period of time enough to form a cartilage layer on the top surface of the matrix block, where the population of MSCs is in an amount enough for the formation of the cartilage layer.

USE - The invention is for promoting growth of cartilage in a patient at a site in need of repair, by implanting an engineered **osteochondral graft** at the site (claimed).

It is used for treatment of **articular cartilage** defects. It might also be applicable in the design of in vitro engineered **articular cartilage** areas, e.g. medial condyle of the femur, for the restoration of an osteoarthritic joint.

ADVANTAGE - The device induces **regeneration** of **articular cartilage**, subchondral bone, and integration of the repaired tissue into the existing host tissue.

DESCRIPTION OF DRAWING(S) - The figure is a representative scanning electron microscopy micrographs of cross-sections of the engineered cell-polymer constructs of cartilage.

Dwg.3/5

ACCESSION NUMBER:	2003-576306 [54] WPIDS
DOC. NO. NON-CPI:	N2003-458100
DOC. NO. CPI:	C2003-155564
TITLE:	Engineered osteochondral grafts for promoting growth of cartilage in patient at defect site in need of repair, comprises matrix block and first population of mesenchymal stem cells forming cartilage layer on top surface of a matrix block.
DERWENT CLASS:	A96 B04 D16 D22 P32
INVENTOR(S):	NOTH, U; TUAN, R S
PATENT ASSIGNEE(S):	(NOTH-I) NOTH U; (TUAN-I) TUAN R S

COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2003050709	A1	20030313	(200354)*		16

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2003050709 A1	Provisional	US 2001-270977P	20010223
		US 2002-82705	20020225

PRIORITY APPLN. INFO: US 2001-270977P 20010223; US 2002-82705 20020225

L6 ANSWER 8 OF 9 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

TI [Aspects of magnetic resonance in the surgical treatment of osteochondral lesions of the knee].
ASPETTI RM DEI TRATTAMENTI CHIRURGICI DELLE LESIONI OSTEOCONDRALI DEL GINOCCHIO.

AB Aim. To assess the magnetic resonance (MR) appearance of knee cartilage chondroplasty procedures and their evolution in order to evaluate the usefulness of the method in monitoring postoperative rehabilitation. Materials and methods. Sixty-two patients treated with knee chondroplasty for high-grade cartilage injuries (Noyes' stages II and III) were examined with MR. Forty patients were treated with abrasion chondroplasty, fifteen with **osteochondral graft** in the injury site and seven with the matrix-induced autologous chondrocyte transplant technique. All patients were operated on by the same orthopaedic team and examined with the same MR protocol. The MR follow-up was performed six months and one year after surgery in the patients treated with abrasion chondroplasty and **osteochondral graft**, and one week, three months and one year after surgery in the patients treated with cartilage transplant. In the patients treated with abrasion chondroplasty we assessed the fibrocartilage repair and the subchondral bone features, in the patients treated with **osteochondral graft** we examined the cartilage, the subchondral bone and the graft borders, while in the patients treated with cartilage transplant we evaluated the features and the evolution of the transplant and the subchondral bone. Arthrosynovitis was assessed in all patients. In seven patients a cartilage repair biopsy was performed in arthroscopy. Results. In all the patients MR imaging proved useful in monitoring the chondroplasty. In the patients treated with abrasion chondroplasty the cartilage repair appeared as a hypointense non-homogeneous irregular strip of tissue that replaced the articular surface. The subchondral bone was sclerotic with some geodes. In the later examination the repair was unchanged. In the patients treated with **osteochondral graft** the **articular cartilage** was similar to the adjacent hyaline cartilage, although more non-homogeneous. The subchondral bone was sclerotic and in three cases oedematous. In four cases the graft extended beyond the articular border. In the cartilage transplant the matrix appeared as a hypointense stripe after a week due to hydration and it had thinned with signal reduction in the later follow-ups. In the cases with unfavourable clinical evolution the subchondral bone was oedematous and sclerotic in the later examinations. In the cases with unfavourable clinical evolution there was moderate arthrosynovitis, regardless of the chondroplasty technique performed. Conclusions. MR imaging is useful for monitoring the maturation and the integration of knee chondroplasty and can be proposed as a replacement of arthroscopy for the assessment of postoperative rehabilitation.

ACCESSION NUMBER: 2003412441 EMBASE
TITLE: [Aspects of magnetic resonance in the surgical treatment of osteochondral lesions of the knee].
ASPETTI RM DEI TRATTAMENTI CHIRURGICI DELLE LESIONI OSTEOCONDRALI DEL GINOCCHIO.
AUTHOR: Macarini L.; Murrone M.; Marini S.; Moretti B.; Patella V.
CORPORATE SOURCE: Dr. L. Macarini, Istituto di Radiologia, Policlinico di Bari, Piazza G. Cesare, 11, 70100 Bari BA, Italy. l.macarini@radiologia.uniba.it
SOURCE: Radiologia Medica, (2003) 106/1-2 (74-86).
Refs: 36
ISSN: 0033-8362 CODEN: RAMEAN
COUNTRY: Italy
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 014 Radiology
027 Biophysics, Bioengineering and Medical Instrumentation
033 Orthopedic Surgery
LANGUAGE: Italian; English
SUMMARY LANGUAGE: English; Italian

L6 ANSWER 9 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI **Regeneration** of **articular cartilage** defects.
ACCESSION NUMBER: 2000:221202 BIOSIS
DOCUMENT NUMBER: PREV200000221202
TITLE: **Regeneration** of **articular cartilage** defects.
AUTHOR(S): Mizuta, Hiroshi [Reprint author]
CORPORATE SOURCE: Dept. of Orthop. Surg., Kumamoto Univ. School of Med., Kumamoto, 860-8556, Japan
SOURCE: Japanese Journal of Pharmacology, (2000) Vol. 82, No. Suppl. 1, pp. 14P. print.
Meeting Info.: 73rd Annual Meeting of the Japanese Pharmacological Society. Yokohama, Japan. March 23-25, 2000.
CODEN: JJPAAZ. ISSN: 0021-5198.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 31 May 2000
Last Updated on STN: 5 Jan 2002

=> s BMP or bone morphogentic protein
L7 20920 BMP OR BONE MORPHOGENTIC PROTEIN

=> d his

(FILE 'HOME' ENTERED AT 15:56:23 ON 02 DEC 2003)

FILE 'MEDLINE, USPATFULL, DGENE, FSTA, WPIDS, HCAPLUS, EMBASE, BIOSIS'
ENTERED AT 15:59:39 ON 02 DEC 2003
L1 426 S BMP-12
L2 5758 S BMP-2
L3 53365 S ARTICULAR CARTILAGE
L4 2094 S L3 AND REGENERATION
L5 119 S OSTEOCHONDRAL GRAFT
L6 9 S L5 AND L4
L7 20920 S BMP OR BONE MORPHOGENTIC PROTEIN

=> s l7 and l5
L8 6 L7 AND L5

=> d l8 ti abs ibib tot

L8 ANSWER 1 OF 6 USPATFULL on STN
TI Trabecular bone-derived human mesenchymal stem cells
AB The present invention discloses an in vitro engineered **osteochondral graft** comprising a porous matrix block, more particularly, a porous polylactic acid polymer block, press-coated with mesenchymal stem cells (MSCs), wherein a cartilage layer is formed on the surface of the matrix block. This invention may be used for treating articular cartilage defects.

ACCESSION NUMBER:	2003:72422 USPATFULL		
TITLE:	Trabecular bone-derived human mesenchymal stem cells		
INVENTOR(S):	Noth, Ulrich, Wurzburg, GERMANY, FEDERAL REPUBLIC OF		
	Tuan, Rocky S., Chester Springs, PA, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003050709	A1	20030313
APPLICATION INFO.:	US 2002-82705	A1	20020225 (10)
	NUMBER		DATE
PRIORITY INFORMATION:	US 2001-270977P		20010223 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	David S. Resnick, NIXON PEABODY LLP, 101 Federal Street, Boston, MA, 02110		
NUMBER OF CLAIMS:	28		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	5 Drawing Page(s)		
LINE COUNT:	852		

L8 ANSWER 2 OF 6 USPATFULL on STN
TI Device for regeneration of articular cartilage and other tissue
AB An implantable device for facilitating the healing of voids in bone, cartilage and soft tissue is disclosed. A preferred embodiment includes a cartilage region comprising a polyelectrolytic complex joined with a subchondral bone region. The cartilage region, of this embodiment, enhances the environment for chondrocytes to grow articular cartilage; while the subchondral bone region enhances the environment for cells which migrate into that region's macrostructure and which differentiate into osteoblasts. A hydrophobic barrier exists between the regions, of this embodiment. In one embodiment, the polyelectrolytic complex transforms to hydrogel, following the implant procedure.

ACCESSION NUMBER:	2003:65819 USPATFULL		
TITLE:	Device for regeneration of articular cartilage and other tissue		
INVENTOR(S):	Brekke, John H., Duluth, MN, UNITED STATES		
	Bradica, Gino, Claremont, NH, UNITED STATES		
	Goldman, Scott M., Paoli, PA, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003045943	A1	20030306
APPLICATION INFO.:	US 2002-199961	A1	20020719 (10)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1998-206604, filed on 7 Dec 1998, GRANTED, Pat. No. US 6264701 Division of Ser. No. US 1994-242557, filed on 13 May 1994, GRANTED, Pat. No. US 5981825		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Alan D. Kamrath, Kensey Nash Corporation, 55 E. Uwchlan Avenue, Exton, PA, 19341		

NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
LINE COUNT: 1263

L8 ANSWER 3 OF 6 USPATFULL on STN
TI Device for regeneration of articular cartilage and other tissue
AB An implantable device for facilitating the healing of voids in bone, cartilage and soft tissue is disclosed. A preferred embodiment includes a cartilage region comprising a polyelectrolytic complex joined with a subchondral bone region. The cartilage region, of this embodiment, enhances the environment for chondrocytes to grow articular cartilage; while the subchondral bone region enhances the environment for cells which migrate into that region's macrostructure and which differentiate into osteoblasts. A hydrophobic barrier exists between said regions, of this embodiment. In one embodiment, the polyelectrolytic complex transforms to hydrogel, following the implant procedure.

ACCESSION NUMBER: 2002:55324 USPATFULL
TITLE: Device for regeneration of articular cartilage and other tissue
INVENTOR(S): Brekke, John H., Duluth, MN, UNITED STATES
Goldman, Scott M., Paoli, PA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002032488	A1	20020314
APPLICATION INFO.:	US 2001-909027	A1	20010719 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-206604, filed on 7 Dec 1998, GRANTED, Pat. No. US 6264701 Division of Ser. No. US 1994-242557, filed on 13 May 1994, GRANTED, Pat. No. US 5981825
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Alan D. Kamrath, Kensey Nash Corporation, 55 E. Uwchlan Avenue, Exton, PA, 19341
NUMBER OF CLAIMS: 56
EXEMPLARY CLAIM: 1
LINE COUNT: 1349

L8 ANSWER 4 OF 6 USPATFULL on STN
TI Scaffold matrix and tissue maintaining systems
AB The invention concerns a scaffold which is used as a growth supportive base for various cells and tissue explants from three-dimensional tissue comprising naturally derived connective or skeletal tissue into attached flakes having a very high porosity. Alternatively the scaffold is composed of fused epiphyses.

ACCESSION NUMBER: 2002:16925 USPATFULL
TITLE: Scaffold matrix and tissue maintaining systems
INVENTOR(S): Nevo, Zvi, Herzliya, ISRAEL
Robinson, Dror, Shimshon, ISRAEL
PATENT ASSIGNEE(S): RAMOT UNIVERSITY AUTHORITY FOR APPLIED RESEARCH & INDUSTRIAL DEVELOPMENT LTD. (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002009805	A1	20020124
	US 6652872	B2	20031125
APPLICATION INFO.:	US 2001-826389	A1	20010404 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-345138, filed on 6 Jul 1999, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LADAS & PARRY, 26 WEST 61ST STREET, NEW YORK, NY, 10023

NUMBER OF CLAIMS: 32
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Page(s)
LINE COUNT: 903

L8 ANSWER 5 OF 6 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
TI Engineered osteochondral grafts for promoting growth of cartilage in patient at defect site in need of repair, comprises matrix block and first population of mesenchymal stem cells forming cartilage layer on top surface of a matrix block.
AN 2003-576306 [54] WPIDS
AB US2003050709 A UPAB: 20030821
NOVELTY - An engineered **osteochondral graft** for promoting the growth of cartilage in a patient at a defect site in need of repair, comprises a matrix block and a first population of mesenchymal stem cells, press-coated on a top surface of the matrix block, and forming a cartilage layer on the top surface of the matrix block, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method of fabricating an **osteochondral graft,** comprising contacting a top surface of a matrix block with a high-density pellet of a population of mesenchymal stem cells (MSCs) for a first period of time enough to form a cell-matrix structure, and culturing the cell-matrix structure in a chondrogenic differentiation medium for a second period of time enough to form a cartilage layer on the top surface of the matrix block, where the population of MSCs is in an amount enough for the formation of the cartilage layer.

USE - The invention is for promoting growth of cartilage in a patient at a site in need of repair, by implanting an engineered **osteochondral graft** at the site (claimed).

It is used for treatment of articular cartilage defects. It might also be applicable in the design of in vitro engineered articular cartilage areas, e.g. medial condyle of the femur, for the restoration of an osteoarthritic joint.

ADVANTAGE - The device induces regeneration of articular cartilage, subchondral bone, and integration of the repaired tissue into the existing host tissue.

DESCRIPTION OF DRAWING(S) - The figure is a representative scanning electron microscopy micrographs of cross-sections of the engineered cell-polymer constructs of cartilage.

Dwg.3/5

ACCESSION NUMBER: 2003-576306 [54] WPIDS
DOC. NO. NON-CPI: N2003-458100
DOC. NO. CPI: C2003-155564
TITLE: Engineered osteochondral grafts for promoting growth of cartilage in patient at defect site in need of repair, comprises matrix block and first population of mesenchymal stem cells forming cartilage layer on top surface of a matrix block.
DERWENT CLASS: A96 B04 D16 D22 P32
INVENTOR(S): NOTH, U; TUAN, R S
PATENT ASSIGNEE(S): (NOTH-I) NOTH U; (TUAN-I) TUAN R S
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2003050709	A1	20030313	(200354)*		16

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2003050709	A1 Provisional	US 2001-270977P	20010223
		US 2002-82705	20020225

PRIORITY APPLN. INFO: US 2001-270977P 20010223; US 2002-82705 20020225

L8 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2003 ACS on STN
TI Cartilage repair
AB A review, on use of growth factors, esp. **BMP**, and surgery (**osteochondral graft**, chondrocyte implantation, etc) in cartilage repair from osteoarthritis and other diseases.
ACCESSION NUMBER: 2002:455217 HCAPLUS
DOCUMENT NUMBER: 137:257721
TITLE: Cartilage repair
AUTHOR(S): Tanaka, Takaaki
CORPORATE SOURCE: Department of Plastic Surgery, Jikei University School of Medicine, Japan
SOURCE: Hone to Nankotsu no Baioroji (2002), 152-156. Editor(s): Fujii, Katsuyuki; Inoue, Hajime. Kanehara Shuppan K.K.: Tokyo, Japan. CODEN: 69CSXM; ISBN: 4-307-25117-2
DOCUMENT TYPE: Conference; General Review
LANGUAGE: Japanese

=> s cartilage regeneration and osteochondral graft
L9 5 CARTILAGE REGENERATION AND OSTEOCHONDRAL GRAFT

=> d l9 ti abs ibib tot

L9 ANSWER 1 OF 5 USPATFULL on STN
TI Tissue maintenance system that applies rhythmic pulses of pressure
AB A growth support scaffold for cells and tissue is formed of naturally derived connective or skeletal tissue which has been treated for elimination of cellular and cytosolic elements, and modified by cross-linking with hyaluronic acid, proteoglycans, glycosaminoglycans, chondroitin sulfates, heparan sulfates, heparins or dextran sulfates. The scaffold may contain cell adhesive molecules and growth factors, and can be formulated as a malleable prosthesis. A tissue maintenance system is provided containing a chamber having a constant atmosphere which may contain the scaffold impregnated with cells, a medium-containing reservoir, a pump which can be computer controlled for circulating the medium between the chamber and reservoir and may change direction of medium flow every 1 to 3 minutes, and a pressure generator, which can be the pump, for producing rhythmic pulses of pressure such as between 0.5 to 30 atm and frequency of 5-300 per minute.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:273353 USPATFULL
TITLE: Tissue maintenance system that applies rhythmic pulses of pressure
INVENTOR(S): Nevo, Zvi, Herzliya, ISRAEL
Robinson, Dror, Shimson, ISRAEL
PATENT ASSIGNEE(S): Ramot at Tel Aviv University Ltd., Ramot Aviv, ISRAEL (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6632651	B1	20031014	
APPLICATION INFO.:	US 1999-345138		19990706	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Naff, David M.
LEGAL REPRESENTATIVE: Ladas & Parry
NUMBER OF CLAIMS: 10

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 11 Drawing Figure(s); 8 Drawing Page(s)
LINE COUNT: 541
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 2 OF 5 USPATFULL on STN
TI Device for regeneration of articular cartilage and other tissue
AB An implantable device for facilitating the healing of voids in bone, cartilage and soft tissue is disclosed. A preferred embodiment includes a cartilage region comprising a polyelectrolytic complex joined with a subchondral bone region. The cartilage region, of this embodiment, enhances the environment for chondrocytes to grow articular cartilage; while the subchondral bone region enhances the environment for cells which migrate into that region's macrostructure and which differentiate into osteoblasts. A hydrophobic barrier exists between the regions, of this embodiment. In one embodiment, the polyelectrolytic complex transforms to hydrogel, following the implant procedure.

ACCESSION NUMBER: 2003:65819 USPATFULL
TITLE: Device for regeneration of articular cartilage and other tissue
INVENTOR(S): Brekke, John H., Duluth, MN, UNITED STATES
Bradica, Gino, Claremont, NH, UNITED STATES
Goldman, Scott M., Paoli, PA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003045943	A1	20030306
APPLICATION INFO.:	US 2002-199961	A1	20020719 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-206604, filed on 7 Dec 1998, GRANTED, Pat. No. US 6264701 Division of Ser. No. US 1994-242557, filed on 13 May 1994, GRANTED, Pat. No. US 5981825
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Alan D. Kamrath, Kensey Nash Corporation, 55 E. Uwchlan Avenue, Exton, PA, 19341
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
LINE COUNT: 1263

L9 ANSWER 3 OF 5 USPATFULL on STN
TI Device for regeneration of articular cartilage and other tissue
AB An implantable device for facilitating the healing of voids in bone, cartilage and soft tissue is disclosed. A preferred embodiment includes a cartilage region comprising a polyelectrolytic complex joined with a subchondral bone region. The cartilage region, of this embodiment, enhances the environment for chondrocytes to grow articular cartilage; while the subchondral bone region enhances the environment for cells which migrate into that region's macrostructure and which differentiate into osteoblasts. A hydrophobic barrier exists between said regions, of this embodiment. In one embodiment, the polyelectrolytic complex transforms to hydrogel, following the implant procedure.

ACCESSION NUMBER: 2002:55324 USPATFULL
TITLE: Device for regeneration of articular cartilage and other tissue
INVENTOR(S): Brekke, John H., Duluth, MN, UNITED STATES
Goldman, Scott M., Paoli, PA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002032488	A1	20020314
APPLICATION INFO.:	US 2001-909027	A1	20010719 (9)

RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1998-206604, filed on 7 Dec 1998, GRANTED, Pat. No. US 6264701 Division of Ser. No. US 1994-242557, filed on 13 May 1994, GRANTED, Pat. No. US 5981825
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Alan D. Kamrath, Kensey Nash Corporation, 55 E. Uwchlan Avenue, Exton, PA, 19341
NUMBER OF CLAIMS:	56
EXEMPLARY CLAIM:	1
LINE COUNT:	1349

L9 ANSWER 4 OF 5 USPATFULL on STN

TI Scaffold matrix and tissue maintaining systems

AB The invention concerns a scaffold which is used as a growth supportive base for various cells and tissue explants from three-dimensional tissue comprising naturally derived connective or skeletal tissue into attached flakes having a very high porosity. Alternatively the scaffold is composed of fused epiphyses.

ACCESSION NUMBER:	2002:16925 USPATFULL
TITLE:	Scaffold matrix and tissue maintaining systems
INVENTOR(S):	Nevo, Zvi, Herzliya, ISRAEL Robinson, Dror, Shimshon, ISRAEL
PATENT ASSIGNEE(S):	RAMOT UNIVERSITY AUTHORITY FOR APPLIED RESEARCH & INDUSTRIAL DEVELOPMENT LTD. (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002009805	A1	20020124
	US 6652872	B2	20031125
APPLICATION INFO.:	US 2001-826389	A1	20010404 (9)

RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1999-345138, filed on 6 Jul 1999, PENDING
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	LADAS & PARRY, 26 WEST 61ST STREET, NEW YORK, NY, 10023
NUMBER OF CLAIMS:	32
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	10 Drawing Page(s)
LINE COUNT:	903

L9 ANSWER 5 OF 5 USPATFULL on STN

TI Multi-stage collagen-based template or implant for use in the repair of cartilage lesions

AB The invention is a template to aid in the regeneration of articular cartilage. The template is formed by combining a porous collagen sponge ("collagen matrix") with a dense collagen membrane. The dense collagen membrane is placed on the surface of the cartilage defect to prevent cell migration from the subchondral plate and vasculature. The collagen membrane will allow movement and exchange of fluids, nutrients, cytokines and other factors necessary for **cartilage regeneration**. The collagen matrix has been developed to allow attachment and growth of cells, specifically chondrocytes which are normally found in articular cartilage. The collagen matrix can be combined with chondrocytes in vitro, and therefore serve to transport cultured cells to the defect site and to retain the cells in position following implantation. Procedures are described to effectively use the two-staged template, and to fix the template to the repair site.

ACCESSION NUMBER:	2000:80202 USPATFULL
TITLE:	Multi-stage collagen-based template or implant for use in the repair of cartilage lesions
INVENTOR(S):	Pachence, James M., Hopewell, NJ, United States

Frenkel, Sally, Flushing, NY, United States
Menche, David, New York, NY, United States
PATENT ASSIGNEE(S): The Hospital for Joint Disease Orthopaedic Institute, New York, NY, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6080194		20000627
APPLICATION INFO.:	US 1995-385290		19950210 (8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Prebilic, Paul B.
LEGAL REPRESENTATIVE: Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd.
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 636

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L5	ligament and L4	101	L5
L4	tendon and L3	125	L4
L3	BMP-2 and L2	406	L3
L2	L1 and articular cartilage regeneration	53211	L2
L1	osteochondral graft and BMP	658	L1

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☐ 1. Document ID: US 6623934 B2

L6: Entry 1 of 25 File: USPT Sep 23, 2003

US-PAT-NO: 6623934
DOCUMENT-IDENTIFIER: US 6623934 B2

TITLE: Bone morphogenetic protein-16 (BMP-16) antibodies

DATE-ISSUED: September 23, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Celeste; Anthony J.	Hudson	MA		
Murray; Beth L.	Arlington	MA		

US-CL-CURRENT: 435/7.1; 530/387.1, 530/387.9, 530/388.1, 530/388.23, 530/388.24, 530/389.1, 530/389.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 6620406 B1

L6: Entry 2 of 25 File: USPT Sep 16, 2003

US-PAT-NO: 6620406
DOCUMENT-IDENTIFIER: US 6620406 B1

TITLE: Methods for treatment of periodontal diseases and lesions using bone morphogenetic proteins

DATE-ISSUED: September 16, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Wozney; John M.	Hudson	MA		
Turek; Thomas J.	Boston	MA		

US-CL-CURRENT: 424/49; 435/252.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 3. Document ID: US 6492493 B2

L6: Entry 3 of 25 File: USPT Dec 10, 2002

US-PAT-NO: 6492493

DOCUMENT-IDENTIFIER: US 6492493 B2

TITLE: Bone morphogenetic protein (BMP)-17 and BMP-18 compositions

DATE-ISSUED: December 10, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Celeste; Anthony J.	Hudson	MA		
Murray; Beth L.	Arlington	MA		

US-CL-CURRENT: 530/350; 530/387.1, 530/387.9

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 4. Document ID: US 6331612 B1

L6: Entry 4 of 25 File: USPT Dec 18, 2001

US-PAT-NO: 6331612
DOCUMENT-IDENTIFIER: US 6331612 B1

TITLE: Bone morphogenic protein-16 (BMP-16) compositions

DATE-ISSUED: December 18, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Celeste; Anthony J.	Hudson	MA		
Murray; Beth L.	Arlington	MA		

US-CL-CURRENT: 530/350; 530/351

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 5. Document ID: US 6328765 B1

L6: Entry 5 of 25 File: USPT Dec 11, 2001

US-PAT-NO: 6328765
DOCUMENT-IDENTIFIER: US 6328765 B1

TITLE: Methods and articles for regenerating living tissue

DATE-ISSUED: December 11, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hardwick; William R.	Flagstaff	AZ		
Thomson; Robert C.	Flagstaff	AZ		
Cleek; Robert L.	Flagstaff	AZ		
Mane; Shrikant M.	Flagstaff	AZ		
Cook; Alonzo D.	Flagstaff	AZ		

US-CL-CURRENT: 623/23.72; 623/23.58, 623/23.76

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 6. Document ID: US 6284872 B1

L6: Entry 6 of 25 File: USPT Sep 4, 2001

US-PAT-NO: 6284872
DOCUMENT-IDENTIFIER: US 6284872 B1

TITLE: Tendon-inducing compositions

DATE-ISSUED: September 4, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Celeste; Anthony J.	Hudson	MA		
Wozney; John M.	Hudson	MA		
Rosen; Vicki A.	Brookline	MA		
Wolfman; Neil M.	Dover	MA		
Thomsen; Gerald H.	Port Jefferson	NY		
Melton; Douglas A.	Lexington	MA		

US-CL-CURRENT: 530/399; 530/350, 530/397, 536/23.1, 536/23.4, 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 7. Document ID: US 6187742 B1

L6: Entry 7 of 25 File: USPT Feb 13, 2001

US-PAT-NO: 6187742
DOCUMENT-IDENTIFIER: US 6187742 B1

TITLE: Method for healing and repair of connective tissue attachment

DATE-ISSUED: February 13, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Wozney; John M.	Hudson	MA		
Rodeo; Scott A.	New York	NY		
Hannafin; Jo A.	New Rochelle	NY		
Warren; Russell F.	Greenwich	CT		

US-CL-CURRENT: 514/2; 514/12, 530/350, 530/399

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 8. Document ID: US 6048964 A

L6: Entry 8 of 25 File: USPT Apr 11, 2000

US-PAT-NO: 6048964
DOCUMENT-IDENTIFIER: US 6048964 A

TITLE: Compositions and therapeutic methods using morphogenic proteins and stimulatory factors

DATE-ISSUED: April 11, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lee; John C.	San Antonio	TX		
Yeh; Lee-Chuan C.	San Antonio	TX		

US-CL-CURRENT: 530/350; 435/235.1, 435/252.3, 435/320.1, 435/325, 435/375, 435/69.1, 530/300, 536/23.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 9. Document ID: US 6034229 A

L6: Entry 9 of 25 File: USPT Mar 7, 2000

US-PAT-NO: 6034229
DOCUMENT-IDENTIFIER: US 6034229 A
**** See image for Certificate of Correction ****

TITLE: BMP-15 compositions

DATE-ISSUED: March 7, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Celeste; Anthony J.	Hudson	MA		
Dube; Jennifer L.	Arlington	MA		
Lyons; Karen M.	Sherman Oaks	CA		
Hogan; Brigid	Brentwood	TN		

US-CL-CURRENT: 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 10. Document ID: US 6034062 A

L6: Entry 10 of 25 File: USPT Mar 7, 2000

US-PAT-NO: 6034062
DOCUMENT-IDENTIFIER: US 6034062 A

TITLE: Bone morphogenetic protein (BMP)-9 compositions and their uses

DATE-ISSUED: March 7, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Thies; R. Scott	Andover	MA		
Song; Jeffrey J.	Brighton	MA		

US-CL-CURRENT: 514/12; 530/350, 530/399, 930/120

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | PwIC | Draw. Desc | Image

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MP52 and L5	25

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DOCUMENT-IDENTIFIER: US 6328765 B1
TITLE: Methods and articles for regenerating living tissue

Brief Summary Text (2):
This invention relates generally to tissue regeneration in a living host. More particularly, the invention relates to tissue regeneration using porous polymeric materials in combination with tissue stimulatory substances.

Brief Summary Text (4):
Surgical options to treat tissue surplus are generally successful in achieving the desired goals of reduced tissue mass and restoration of normal tissue geometry. Procedures of this nature include ostectomy, mastectomy, partial and complete hepatectomy. However, when tissue deficiencies are present and there is a need or desire to increase tissue mass, therapeutic options become more involved, and less certain in outcome. Options to increase tissue mass include the use of autografts, allografts, xenografts and alloplastic materials. Autografts involve the transfer of tissue from one part of the patient to another (either as a vascularized graft or as a non-vascularized graft). The main drawbacks of autograft therapies are; the limited amount of tissue that is available for transfer, donor site morbidity and, in some cases, the complete lack of available or appropriate donor sites. In addition, in the case of non-vascularized bone grafts, resorption of the transferred tissue can result in decreased tissue mass and inadequate function and/or aesthetic outcome.

Brief Summary Text (6):
Much attention has been paid to the possibilities of generating or regenerating tissues. In the case of tissues which have some potential for self-regeneration (such as bone, cartilage and nerve), porous matrices, which are usually biodegradable, have been used to direct tissue formation. However, these regenerative processes are dependent on, and limited by, both device design and the regenerative potential inherent in the biological processes of the individual. This dependence may affect rate of formation, quantity and architecture of the resulting tissue. In the case of bone, porous materials, such as coralline hydroxyapatite and certain preparations of allograft bone, have been used as scaffolds to facilitate tissue growth into bony defects. This approach has been successful in instances associated with small defects but lacks the desired predictability of outcome in many clinically relevant large defects. Interaction of the host cells, e.g. the so called foreign body reaction, with the porous matrix also may limit the rate, quantity and architecture of the tissue formed within the device.

Brief Summary Text (7):
Recent research has also focused on the use of bioactive molecules or transplanted cells that have the potential to stimulate tissue formation. The local administration of cells or bioactive molecules alone is insufficient and does not result in predictable regeneration of tissue masses (Bessho 1996). Research efforts have therefore focused on the use of carriers to deliver bioactive molecules or act as scaffolds for transplanted cells. In addition the carriers act as scaffolds to direct cell growth and tissue formation. Such carriers usually take the form of space filling devices, such as three-dimensional porous networks, gels, microspheres or granular materials. Membranes which create and maintain a space for tissue regeneration have also been used as carriers for bioactive molecules.

Brief Summary Text (8):

Space filling devices have been used extensively in the field of bone regeneration to act as carriers for bioactive molecules known to stimulate bone formation (Wolfe and Cook, 1994). The materials used to fill a space where bone formation is required vary widely in their structural geometry and mechanical properties and include porous hydroxyapatite, allograft bone, collagen sponge and degradable polymer foams, scaffolds (Brekke, U.S. Pat. No. 5,683,459) and microspheres. These various approaches to bone regeneration each suffer one or more drawbacks.

Brief Summary Text (10):
Many of these problems may be circumvented through the use of carriers such as collagen sponges which do not appear to significantly interfere with tissue formation or remodeling even during the degradation phase of the material. For example, Ksander et al. (U.S. Pat. No. 4,950,483), Chu et al. (U.S. Pat. No. 5,024,841) and Chu et al. (U.S. Pat. No. 5,219,576) describe a space filling collagen sponge with pores greater than 35 microns which may be used in conjunction with bioactive agents to promote wound healing. However, collagen sponges, especially those with suitable degradation time frames, are generally not able to withstand the above-listed in vivo stresses and consequently are unable to maintain the size and shape of the filled space. As a result, the newly created tissue assumes an ill-defined geometry which is not the same as the original shape of the sponge and which is often not of adequate or optimal functional or therapeutic benefit. Such an outcome is reported by Oppermann et al. (U.S. Pat. No. 5,354,557) who describes the use of a collagen sponge combined with osteogenic proteins for bone regeneration. Wolfe and Cook (1994) have also recognized the difficulty of controlling the geometry of bone formed using osteogenic proteins and state that "the osteoinductive effect of the protein can be difficult to confine to a limited anatomic area, especially using semi-solid carrier vehicles." This same phenomenon can be seen with degradable synthetic polymer structures that, although they can be designed with appropriate mechanical stresses at the time of implantation, gradually lose their ability to withstand in vivo stresses and collapse at some point during degradation.

Brief Summary Text (11):
Kuboki et al. (1995) used bioactive molecules in conjunction with a flat, space-filling, unwoven glass fibril membrane to study bone formation. In this case, the majority of the tissue formed was cartilage that was located within the microstructure of the membrane. The desired bone tissue was therefore not formed and the cartilage tissue generated was associated with a non-degradable material that is likely to adversely influence the desirable properties of the natural tissue. Chu et al. (U.S. Pat. No. 5,219,576) describe a space filling collagen matrix with a thickness of 1-20 mm and a pore size of at least 30 mm in diameter. The matrix is intended for use in skin/dermal wound healing and tissue regeneration and can be used in conjunction with bioactive molecules. The teachings of Chu et al. do not address the necessity of controlling the configuration of the tissue generated by the articles and methods of the invention.

Brief Summary Text (12):
An improvement of these tissue regeneration methods is found in the field of guided tissue regeneration. Guided tissue regeneration is a therapeutic approach aimed at regenerating periodontal tissues and bone, particularly of the jaw. It is based on the concept of selective tissue exclusion and attempts to optimize the natural regenerative potential of the patient's tissues. Exclusion of undesirable fibrous tissue from the regenerative space is achieved through the use of a membrane that acts as a passive physical barrier which is substantially impermeable to cells and tissues. In addition, the membrane maintains the regenerative space until such time as the tissue is regenerated. This technology has done much to advance the field of alveolar bone and periodontal tissue regenerative therapies, however, the widespread application of this technology has not been fully realized due to issues of predictability in the most clinically challenging situations.

Brief Summary Text (13):
Scantlebury et al. (U.S. Pat. No. 5,032,445) described the potential for a combination of tissue excluding guided tissue regeneration membranes and bioactive molecules. This concept was reiterated by Golgolewski (U.S. Pat. No. 5,676,699 and EP 0 475 077) who described a degradable, microporous bone regeneration membrane

which may be used in conjunction with various bioactive molecules. Again, the membrane was used as a "tissue separator which promotes and protects osseous regeneration." According to Golgolewski, the essential function of the micropores is that they are "permeable for nutritional fluids." This statement is consistent with the most preferred pore diameter range of 0.1 to 5.0 mm. Similar concepts have been reported by Sottosanti (U.S. Pat. No. 5,569,308), Dunn et al. (U.S. Pat. No. 5,077,049), Jernberg (U.S. Pat. No. 5,059,123 and U.S. Pat. No. 5,197,882) and Hehli (U.S. Pat. No. 5,383,931). Saffran (U.S. Pat. No. 5,446,262) for example, describes a two layered, tissue excluding membrane for the directional delivery of bioactive molecules for tissue repair. A bi-layered tissue excluding membrane in combination with a bioactive molecule is also described by Aebischer et al. (U.S. Pat. No. 5,011,486) for nerve regeneration.

Brief Summary Text (14):
The combination of bioactive molecules with guided tissue regeneration membranes has also been studied in small, experimental defects in rabbit long bones by Zellin and Linde (1997). In this model the combination of a bioactive molecule with a cell and tissue excluding membrane was successful in regenerating the bone defect. However, studies by Cochran et al. (1997) show that bone formation in the mandible is impeded by the use of a cell and tissue excluding membrane in combination with a bioactive molecule. In addition, studies by Hedner and Linde (1995) found that the combination of a cell and tissue excluding membrane and a bioactive molecule was less effective in stimulating bone healing in mandibular defects than the bioactive molecule alone. Predictable bone regeneration using a bioactive molecule and a membrane which excludes cells and tissue from the regenerative space has yet to be shown.

Brief Summary Text (18):
The use of membranes which are not tissue excluding has been studied by Pineda et al. (1996) for long bone regeneration. This study showed that the principles and mechanisms of guided bone regeneration do not operate when membranes are utilized with larger pore sizes that do not result in cell and tissue exclusion. Consequently, significantly less bone regeneration results with large pore size membranes which do not exclude cells and tissue. Haris (U.S. Pat. No. 4,787,906) describes a similar system for alveolar ridge augmentation which utilizes inert particles contained within a porous tube designed to allow tissue through growth. The teachings of Haris specify fibrovascular invasion into the tube, but this invention does not teach the use of bone inductive agents.

Brief Summary Text (19):
Tepic (U.S. Pat. No. 5,211,664 and EP 0 551 611) teaches the use of a structure for long bone regeneration which comprises two concentric, parallel, tubular shells connected to each other by struts. One or both of the shells may be provided with interconnected micropores and therefore, according to the author, "diffusion alone is sufficient to maintain grafted metabolism in the critical phase before revascularization takes place." The author further states that the shells of the concentric tubular structure may also have "larger openings in the range of 0.1 to 2.0 mm" which "allow for vascular ingrowth from surrounding tissue." However, the author espouses adherence to the above-summarized teachings of guided tissue regeneration in which a membrane or sheet structure is used to substantially exclude soft tissue and soft tissue ingrowth from the space created by the membrane. Indeed, the most preferred embodiments are consistent with the teachings of guided tissue regeneration and stipulate the use of a concentric membrane structure with pore diameters in the range 0.1 to 5.0 mm. The structure is also intended to serve as a container for bone grafts or various bioactive agents.

Brief Summary Text (20):
The use of macroporous membranes in conjunction with autograft bone for long bone regeneration has been studied by Gerber and Golgolewski (1996) and later by Gugala and Golgolewski (1997). In these studies, a long bone defect was filled with autograft bone and covered with a macroporous membrane. Although these studies showed that it is possible to regenerate bone in this manner, this approach also resulted in massive resorption of the graft. In order to ameliorate the undesirable resorption outcome, two concentric macroporous membranes were required; one inserted into the medullary canal and the other placed on the periphery of the defect with the annular space filled with autograft bone. It is clear that long bone defects do

not heal appropriately in the long term using a combination of autograft bone and a single macroporous membrane. Furthermore, in order to appropriately utilize the regenerative potential of autograft bone in long bone defects a highly specific device design involving concentric macroporous membranes is required. An additional drawback of this methodology is that it requires the use of autologous tissue in quantities at least sufficient to fill the defect.

Brief Summary Text (21):
Lemperle et al. (1996) has studied the use of a titanium mesh as a containment system for autograft bone. These studies have shown that with this system, it is possible to regenerate only as much bone over a 4 month period as is regenerated using a titanium mesh placed over an empty defect. Holmes (1997) has also postulated the use of a resorbable macroporous sheet as a containment system for bone grafts and Patyk (DE 91 15 341) describes a similar system for bone substitute materials. However, as the studies of Gugala and Golgolewski show, the use of a single macroporous sheet in conjunction with autograft bone does not result in a satisfactory long term healing response at least for long bone applications. In addition, this approach also requires the use of autologous tissue to fill the defect.

Brief Summary Text (22):
Teixeira and Urist (1997) describe the use of macroporous membrane, with pores 0.5 mm in diameter, in conjunction with a mixture of bovine derived bone morphogenetic protein and associated non-collagenous bone matrix protein for long bone regeneration.

Brief Summary Text (23):
Lemperle (WO 98/07384) describes a macroporous membrane structure for tissue reconstruction. The reference teaches that regeneration of bone and other tissues may be achieved solely through the use of a macroporous membrane which prevents prolapse of the surrounding soft tissue and allows ingrowth of blood vessels and connective tissue. However, as the long bone regeneration studies of Pineda et al. (1996) show, the principles and mechanisms of guided bone regeneration do not operate when membranes are utilized with larger pore sizes that do not result in cell and tissue exclusion. Significantly less bone regeneration results with large pore size membranes which do not exclude cells and tissue.

Brief Summary Text (24):
Although the Lemperle reference focuses on the merits of the macroporous membrane structure in tissue and bone regeneration, mention is also made of the possibility of impregnating the membrane with substances for promoting the regeneration of different tissues such as bone and blood vessels. Although delivery of a bioactive substance from a membrane may appear to be an attractive proposition, there are significant biological and technical shortcomings of this approach. It is technically difficult to achieve delivery of therapeutically effective quantities of an appropriate bioactive molecule from a membrane. For example, it is not always possible to load sufficient quantities of a bioactive agent onto a membrane by relying on simple adsorption of the molecules onto the membrane surface, especially if the membrane is constructed from a hydrophobic material. Materials which are hydrophobic in nature are most often used to construct membranes since they have superior mechanical properties over hydrophilic materials such as collagen.

Brief Summary Text (26):
In addition to the technical difficulties involved in achieving appropriate delivery of a bioactive agent from a membrane, it has not been shown that delivery of a bioactive molecule from a macroporous and tissue penetrable membrane surrounding the periphery of a tissue defect is efficacious in regenerating a desired tissue. The presence of macropores in the membrane allows diffusion of the bioactive molecule both inward toward the center of the defect and outward toward the surrounding soft tissue. This has two distinct disadvantages. First, the presence of the bioactive molecule in high concentrations near the outer surface of the membrane would be likely to cause the desired tissue to form on the outside of the membrane thus resulting in a lack of control of the regenerated tissue geometry. Second, diffusion of the bioactive molecule inward toward the center of the defect would result in an adverse concentration gradient for the migration of cells, such as mesenchymal stem

cells, from the tissue surrounding the defect. The migration of cells in response to a local concentration gradient is known as chemotaxis and is normally associated with cellular migration toward the highest concentration of a chemotactic substance. In the case of membrane delivered bioactive molecules, the lowest concentration would be at the center of the defect and the highest concentration at the surface of the membrane. Mesenchymal stem cells would therefore be expected to migrate toward the membrane and not toward the center of the defect where they are needed to facilitate tissue regeneration.

Brief Summary Text (27):
In summary, studies have been performed which utilize non-macroporous, tissue excluding membranes in conjunction with bioactive agents (Cochran et al. (1997) and Hedner and Linde (1995)). In each case, a bioactive agent delivered in an appropriate manner from a carrier material filling the space under a tissue excluding membrane did not achieve the desired bone regeneration result. In addition, desired bone regeneration is not attained when a macroporous membrane, which does not result in cell and tissue exclusion, is used alone (Pineda et al. (1996)). Although impregnating a macroporous membrane with bioactive molecules (Lemperle (WO 98/07384)) may result in bone formation, the regenerated tissue is unlikely to conform to the desired configuration defined by the geometry of the membrane.

Detailed Description Text (11):
Generation here means the production, restoration or regeneration of living tissue within the body of a mammal. Living tissue here refers to the level of biological organization above that of a simple aggregation of similar type cells. Living tissue is composed of similar and associated cells and intercellular substance with specific organization and processes important to the functioning, appearance, and well-being of the mammal. Most living tissues include multiple cell types and structures. For example, the major components of bone tissue include bone cells that are generally located within a matrix of mineralized collagen; blood vessels that provide nutrition for the bone cells; and may include fatty bone marrow and/or cells that give rise to components of the blood.

Detailed Description Text (33):
Additionally, materials may be placed in the established space that serve as a scaffold for the migration of cells and blood vessels originating from the living tissue of the mammal during the generation process. This scaffold may be as simple as blood coagulum which fills the space in the normal coarse of events following implantation of the TP device. Alternatively, the scaffold may be provided as part of the method and kit of the present invention and may include such known substances as collagen, hyaluronic acid, porous or particulate calcium phosphate or calcium carbonate. Materials may also be positioned within the established space in order to direct the functional structure of the living tissue being generated. For example, functional structure in ligaments and tendons is provided by longitudinally oriented fibroblasts and collagen bundles. Longitudinally oriented collagen or hyaluronic acid fibers may be positioned in the space established by the device of the present invention to direct the orientation of fibroblast cells and the collagen matrix produced by the fibroblast cells with the result being the generation of a tendon or ligament.

Detailed Description Text (34):
A necessary component to this method of generating desired living tissue with desired configuration within a mammal is by providing, within the space established by the TP device, one or more molecular substance able to initiate, stimulate, and/or support, directly or indirectly, the growth and development of desired living tissues. These molecular substances are herein referred to as tissue stimulatory molecular substances (TSMS). TSMS does not include such things as autogenic, allogenic, or xenogenic tissue grafts as these contain a generally uncharacterized multiplicity of cellular and non-cellular substances, in some cases including potential pathogenic organisms. The TSMSs must be provided in ways and in forms that they are accessible to and able to stimulate the specific target cells, tissues, and physiological systems of the mammal necessary for generation of desired living tissue. The TSMSs may be provided in a purified or partially purified form, having been produced outside the mammal being treated. The TSMSs may be produced by a

number of methods including, but not limited to, recombinant protein technologies, chemical processes, pharmaceutical processes or tissue extraction processes. Tissue extracted TSMSs may be derived from xenogeneic, allogeneic, or autogeneic tissues including, but not limited to, bone, cartilage, dentin, liver, bone marrow or blood. The extraction method should remove a substantial portion of the cellular and non-TSMS components of the tissue. Alternatively, the TSMSs may be produced by cells that have been modified to produce the TSMSs and which are placed within the space at the time of implantation. Cryopreservation is one method of providing the above-described cells.

Detailed Description Text (36):
TSMSs known to exert desired differentiation, mitogenic, chemotactic, or matrix synthesis effects on cells are dimers of Platelet Derived Growth Factor (PDGF), insulin-like growth factor-1 (IGF-1), IGF-2, basic Fibroblast Growth Factor (bFGF), acidic FGF, Vascular Endothelial Cell Growth Factor (VEGF), Endothelial Growth Factor (EGF), Insulin, Interleukin 1 (11-1), Tumor Necrosis Factor alpha (TNF-.alpha.), Connective Tissue Growth Factor (CTGF), Transforming Growth Factor-.alpha. (TGF-.alpha.), para-thyroid hormone (PTH), prostaglandins (PGE), Macrophage-Colony Stimulating Factor (MCSF), corticosteroids (such as dexamethasone, prednisolone, corticosterone), and various members of the Transforming Growth Factor-.beta. (TGF-.beta.) superfamily of proteins including TGF-.beta.1, TGF-.beta.2, Bone Morphogenetic Protein-2 (BMP-2) disclosed in U.S. Pat. No. 5,013,649, BMP-1, BMP-3, BMP-4, BMP-5, BMP-6 and BMP-7 (disclosed for instance in U.S. Pat. Nos. 5,108,922, 5,013,649, 5,116,738, 5,106,748, 5,187,076, and 5,141,905), BMP-8 (disclosed in U.S. Pat. No. 5,688,678), BMP-9 (disclosed in U.S. Pat. No. 5,661,007), BMP-10 (disclosed in U.S. Pat. No. 5,703,043), BMP-11 (disclosed in U.S. Pat. No. 5,639,638), BMP-12 or BMP-13 (disclosed in U.S. Pat. No. 5,658,882), BMP-15 (disclosed in U.S. Pat. No. 5,635,372). Other proteins which may also be useful include Vgr-2, and any of the growth and differentiation factors [GDFs], including those described in U.S. Pat. No. 5,808,007 [GDF-3], U.S. Pat. No. 5,801,014 [GDF-5], and U.S. Pat. No. 5,821,056 [GDF-9], as well as PCT applications WO95/01801 [GDF-6], WO95/01802 [GDF-7], WO94/21681 [GDF-8], WO95/10539 [GDF-10], WO96/01845 [GDF-11], WO96/02559 [GDF-12] and others. Also useful in the present invention may be BIP (disclosed in WO94/01557) and MP52 (disclosed in PCT application WO93/16099). The disclosures of all of the above applications are hereby incorporated by reference.

Detailed Description Text (41):
The types of desired living tissue that can be generated utilizing this invention may be specific, as in the case of bone, or may include structures composed of more than one type of tissue but which provide a functional purpose, for example periodontal support structures (those tissues anchoring and supporting the teeth), which are composed of the alveolar bone of the jaw, the periodontal ligament, and the tooth root cementum.

Detailed Description Text (42):
Tissues that may be generated using the methods and components of this invention include, but are not limited to, bone tissue, periodontal tissues, adipose (fat) tissue, tendon tissue, ligament tissue, hyaline cartilage tissue, articular cartilage tissue, muscle tissue, and connective tissue.

Detailed Description Text (52):
Studies have demonstrated that alveolar bone and cementum regeneration appears critically dependent on the establishment of a space within the body of the mammal being treated. This space is established by the surgical placement of a tissue-excluding (TE) membrane device that functions as a passive barrier to prevent ingrowth of fibrous connective tissue and establishes a space into which bone or periodontal tissues are desired to grow. It has been previously shown that in the canine critical-sized periodontal defect model described by Wikesjo and Nilveus (J Periodontal 1991;18:49-59), non-reinforced TE ePTFE membrane devices exhibit a tendency to collapse in response to pressure from the overlying soft tissue, with concomitant reduction in the volume of established space. TE devices are membranes with small pore size that substantially prevent tissue through-growth originating from soft tissues outside the boundary established by the membrane. Critical size defects do not spontaneously regenerate over the lifetime of the animal without some

type of significant intervention. When collapse of the space is virtually complete, little or no bone regeneration occurs. In situations where collapse is incomplete and a limited volume of space is established, alveolar bone regeneration progresses and fills most of the space available within a four week period following surgery (Haney et al. J Periodontal 1993;883-890). In the presence of a larger volume space established with a shaped and reinforced membrane shell, the alveolar bone assumes a "physiologic" form adapting to the tooth surface averaging 75% of a 5 mm supraalveolar periodontal defect. The remainder of the wound space is filled by dense fibrous connective tissue (Sigurdsson et al. J Periodontal 1994;65:350-356). Inherent regeneration potential in critical size periodontal defects appears to be limited in amount although it can be significantly enhanced by TE membranes. In addition, the conformation of periodontal structures cannot be controlled by relying only on the inherent biological potential of the individual. No information has been available in this model on the inherent regenerative potential using membranes with pores large enough to allow tissue through-growth.

Detailed Description Text (54):
Periodontal Tissue Regeneration with Tissue Exclusive and Tissue Penetrable Devices.

Detailed Description Text (57):
It is hypothesized that use of a TP device, capable of allowing penetration of vascular structures and soft tissue cells into the established space, will result in regeneration of periodontal structures equivalent to TE devices.

Detailed Description Text (84):
New bone regeneration is measured by the following methods. A Mitutoyo.TM. metric dial caliper (accuracy .+-.0.01 mm) is used to make the measurements directly from the radiographs. The following parameters are measured:

Detailed Description Text (87):
An index (I) is calculated for the relative amount of interproximal bone regeneration for each tooth and each quadrant. This index is calculated by dividing the IP value by D for each tooth. This method allows for comparison of specimens taking into account possible differences in angulation of the tissue block relative to the direction of X-rays and/or the radiographic film. Mean "I" values, and standard deviations of the mean, are calculated for each experimental group (TP and TE) and each tooth group (e.g. TP;P3 and TP;P4).

Detailed Description Text (88):
Qualitative observations of the histological glass slides are also made. The most central stained section of each root for the third and fourth premolar teeth is identified by the size of the root canal. Sections were evaluated for bone regeneration.

Detailed Description Text (98):
In this model system, simply coronal positioning and suturing of the soft tissue flaps, without placement of either TE or TP devices, shows very limited potential for alveolar bone regeneration (Wikesjo et.al., J Periodontal 1994;65:1151-1157).

Detailed Description Text (99):
In this study only one of six TE sites remained non-symptomatic for the eight week healing period, with three of six sites requiring early removal due to exposure and infection. The single non-exposed, non-symptomatic TE site exhibited a new bone index of 0.96. The remaining five sites that exhibit some type of inflammatory complication show a range of new bone indices from 0.32 to 0.61 with a mean of 0.48. This is consistent with a previous study using TE devices in this model, where investigators concluded that exposure and infection of TE sites compromise periodontal regeneration (Sigurdsson et.al., J Periodontal 1994;65:350-356). In addition, Sigurdsson et.al. found that non-compromised TE sites exhibited approximately 75% of alveolar bone regeneration (corresponding to a new bone index of 0.75).

Detailed Description Text (102):
These results suggest that treatment with TP devices have an increased regenerative

potential compared to treatment without devices, and reduced regenerative potential compared to TE devices. These observations are consistent with the concept of Guided Tissue Regeneration that states that fibrous connective tissue cells originating from the gingival connective tissue have the potential to interfere with alveolar bone regeneration in periodontal defects. The TP devices, by virtue of the nominal 300 micrometer laser-drilled holes, allow fibrous connective tissue cells to have access to the space established by surgical implantation of the device. Neither TE nor TP sites regenerated periodontal tissue with configuration determined by the configuration of the device.

Detailed Description Text (150):
Following euthanasia, block sections including teeth, bone, soft tissues, and implanted materials are removed using sharp dissection and a reciprocating bone saw (Stryker) and radiographed to estimate bone regeneration. The block sections are rinsed in cool tap water and placed in 10% buffered formalin for a minimum of five days.

Detailed Description Text (155):
All animals evaluated exhibited non-complicated healing during the eight week in-life period. Radiographically controls (TP+ACS+buffer) show substantially less bone regeneration (approximately 25%) compared with the test sites (TP+ACS+rhBMP-2), all four of which exhibit 100% bone height formation, and virtually complete fill of the space established by the TP ePTFE devices (Table B). The new bone formation takes the arch shaped configuration of the devices, FIG. 14, Group I. Little to no bone formation is observable on the outside of the device in test sites.

Detailed Description Text (173):
In all cases sites treated with the TP device and rhBMP-2 (TP+ACS+rhBMP-2) show bone regeneration to a level of 100% or greater of the defect height (Table B). Bone tissue has largely filled the space within the TP device when rhBMP-2 is present, even though the protein is not completely distributed throughout the established space (Table B, Group II). The shape of the bone formation induced by the protein takes on the arch shaped configuration of the devices and the configuration is controlled by the shape of the device, with little to no bone formation taking place outside the space established by the device.

Detailed Description Text (174):
Sites treated with ACS+rhBMP-2 show bone regeneration to the level of the CEJ or above (.gtoreq.100% of defect height) (Table B, Group II). However, the cross-sectional shape of the ridge varies considerably from site to site, and the overall arch shape of a normal alveolar ridge is not predictably attained (FIG. 14, Group II). Instead, the cross-sectional shape of the regenerated bone is roughly triangular.

Detailed Description Text (214):
When no rhBMP-2 is provided in the established space, use of TP devices appears, at best, to achieve no better regenerative result than TE devices. In fact, the evidence from Example 1 suggests that while TP devices appear to enhance periodontal bone regeneration, compared to published information from the canine supraalveolar critical size periodontal model without device placement, regenerative capacity may be somewhat decreased compared to treatment with TE devices. In neither TP nor TE sites without rhBMP-2 is the configuration of regenerated periodontal bone controlled (Example 1).

Detailed Description Text (215):
In contrast, sites treated with the TP device and rhBMP-2, whether or not the protein was distributed entirely throughout the established space, show bone regeneration to a level of 100% of the tooth or dental implant height (Table B). Of greatest importance is the observation that bone tissue had largely filled the available space with the TP devices when rhBMP-2 was placed within the space (Table B, and FIG. 14). Significantly the shape of bone formation induced by the protein was determined by the shape of the device, with little to no bone formation having taken place outside the space established by the device. This was true for both periodontal and peri-implant sties. Thus, the shape and volume of the new bone formed by the activity of the rhBMP-2 was determined closely by the configuration of

the device. In 15 out of 16 sites, the shape of bone formation induced by the protein exhibits the arch configuration provided by the configuration of the TP ePTFE devices. It is estimated that in the 15 sites with controlled configuration, greater than about 80% of the established space is newly generated living bone tissue.

Detailed Description Text (216):
Control sites treated with TP devices and ACS but without rhBMP-2 show substantially less bone regeneration compared with either the TP+ACS+rhBMP-2 sites, or the ACS+rhBMP-2 sites (Examples 3, 4, 5, and 6). This was true for periodontal defects (25%) and peri-implant sites (10%).

Detailed Description Text (217):
Periodontal sites treated with rhBMP-2 +ACS, but without TP devices show bone regeneration to the level of the CEJ or above. However, the cross-sectional shape of the ridge varies considerably from site to site, the volume of new bone formed is generally less than sites treated with TP ePTFE devices and rhBMP-2, and the overall arch shape of a normal alveolar ridge is not predictably attained.

Detailed Description Text (293):
Qualitative radiographic observations indicate substantial bone formation in test sites at 4 weeks post surgery. There is a general increase in density of bone over the 8 week and 24 week time periods. There is also a very slow decrease in bone height over time although in no cases does this progress below the cemento-enamel junction of the teeth. CT scans indicate some variability in new bone configuration, however, the scans do show substantial bone regeneration in the test sites. In general, the configuration of bone is not controlled as well as observed in Examples 3, 4, 5, and 6.

Detailed Description Paragraph Table (1):
TABLE A NEW BONE REGENERATION INDICES TISSUE PENETRABLE AND TISSUE EXCLUSIVE SITES GROUP TP TE K9 # I-P3 I-P4 Mean I-P3 I-P4 Mean 7591 0.93 0.77 0.85 0.34 0.32 0.32 7592 0.65 0.57 0.61 0.64 0.62 0.62 7593 0.45 0.47 0.46 0.46 0.41 0.41 7594 0.74 0.64 0.69 0.62 0.60 0.61 7595 0.43 0.38 0.40 1.02 0.90 0.96 7596 0.61 0.56 0.59 0.50 0.39 0.45 Mean .+-. 0.64 .+-. 0.57 .+-. 0.60 .+-. 0.60 .+-. 0.52 .+-. 0.56 .+-. S.D. 0.19 0.13 0.16 0.23 0.22 0.23 TP - Tissue-Penetrable devices TE - Tissue-Exclusive devices I - Index; Interproximal bone height .div. Mean defect height P3 - mandibular 3rd premolar P4 - 4th mandibular premolar

Other Reference Publication (6):
Gugala Z and Gogolewski S. Regeneration of Bone in Large Segmental Diaphyseal Defects Using Tube-in-Tube Resorbable Polymeric Implants. 23.sup.rd Annual Meeting of the Society for Biomaterials. Apr. 30-May 4, 1997.

Other Reference Publication (7):
Hedner E, Linde A. Efficacy of bone morphogenetic protein (BMP) with osteopromotive membranes-an experimental study in rat mandibular defects. Eur J Oral Sci 1995; 103: 236-241.

Other Reference Publication (8):
Holmes RE et al. A macroporous Protective Sheet for Bone Regeneration and Implant Containment. Presented at IBC's First Annual International Conference on Orthopaedic Biomaterials. San Diego, CA. Dec. 11-12, 1997.

Other Reference Publication (10):
Kuboki Y et al. Two Distinctive BMP-Carriers Induce Zonal Chondrogenesis and Membranous Ossification, Respectively; Geometrical Factors of Matrices for Cell-Differentiation. Connective Tissue Research 1995; 32(1-4) 219-226.

Other Reference Publication (11):
Lemperle SM et al. Comparison of Protected Bone Regeneration, Osteoconduction with Coralline Hydroxyapatite Implants, and Cancellous Bone Autografts in Large Cranial and Mandibular Defects in Dogs. Surgical Forum 1996; 47:723-727.

Other Reference Publication (12):

Pineda LM et al. Bone regeneration with resorbable polymeric membranes. III. Effect of poly(1-lactide) membrane pore size on the bone healing process in large defects. Jou Biomedical Materials Research 1996; 31:385-394.

Other Reference Publication (13):
Spector, M. Ceramic Materials and Bone Regeneration. Presented at the Bone Symposium at Orecon Health Sciences University. Jul. 17-20, 1991.

CLAIMS:

26. The method of claim 1 wherein said desired living tissue is selected from the group consisting of periodontal tissue, connective tissue, muscle tissue, bone tissue, tendon tissue, ligament tissue, cartilage tissue, and adipose tissue.

30. The method of claim 1 wherein said desired living tissue comprises cartilage tissue.

31. The method of claim 1 wherein said desired living tissue comprises tendon tissue.

32. The method of claim 1 wherein said desired living tissue comprises ligament tissue.

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L3: Entry 1 of 1 File: USPT Oct 26, 1999

DOCUMENT-IDENTIFIER: US 5972368 A
TITLE: Bone graft composites and spacers

Abstract Text (1):
A bone graft substitute including a composition of natural selectively deactivated bone material which has been processed to remove associated non-collagenous bone proteins, said bone material containing native collagen materials and naturally associated bone minerals and substantially free from native non-collagenous protein, and a therapeutically effective amount to stimulate bone growth of a bone growth factor in a pharmaceutically acceptable carrier in synergistic combination with said bone material. Spacers composed of the bone graft substitute composition methods for using the spacers are also provided.

US Patent No. (1):
5972368

Brief Summary Text (2):
The present invention relates to bone graft substitute materials and spacers composed of the materials for arthrodesis. In specific applications of the invention the materials are provided in synergistic combination with osteogenic compositions.

Brief Summary Text (5):
An osseous bridge, or fusion mass, is biologically produced by the body upon skeletal injury. This normal bone healing response is used by surgeons to induce fusion across abnormal spinal segments by recreating spinal injury conditions along the fusion site and then allowing the bone to heal. A successful fusion requires the presence of osteogenic or osteopotential cells, adequate blood supply, sufficient inflammatory response, and appropriate preparation of local bone. This biological environment is typically provided in a surgical setting by decortication, or removal of the outer, cortical bone to expose the vascular, cancellous bone, and the deposition of an adequate quantity of high quality graft material.

Brief Summary Text (9):
Bone grafts are often used to fill the intervertebral space to prevent disc space collapse and promote fusion of the adjacent vertebrae across the disc space. In early techniques, bone material was simply disposed between the adjacent vertebrae, typically at the posterior aspect of the vertebrae, and the spinal column was stabilized by way of a plate or rod spanning the affected vertebrae. Once fusion occurred the hardware used to maintain the stability of the segment became superfluous and was a permanent foreign body. Moreover, the surgical procedures necessary to implant a rod or plate to stabilize the level during fusion were frequently lengthy and involved.

Brief Summary Text (11):
Many attempts to restore the intervertebral disc space after removal of the disc have relied on metal devices. U.S. Pat. Nos. 4,878,915 to Brantigan teaches a solid metal plug. U.S. Pat. Nos. 5,044,104; 5,026,373 and 4,961,740 to Ray; 5,015,247 to Michelson and U.S. Pat. No. 4,820,305 to Harms et al., U.S. Pat. No. 5,147,402 to Bohler et al. and 5,192,327 to Brantigan teach hollow metal cage structures. Unfortunately, due to the stiffness of the material, some metal implants may stress shield the bone graft, increasing the time required for fusion or causing the bone

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L14	L13 and l11	1	L14
L13	bmp or bone morphogenic protein	183184	L13
L12	L11 and l7	1	L12
L11	5750651.pn.	1	L11
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L9	cartilage	8926	L9
L8	L7 and l1	1	L8
L7	cartilage regeneration	53205	L7
L6	5972368.pn. and cartilage regeneration	45708	L6
L5	cartilage regeneration and l1	8927	L5
L4	articular cartilage and l1	5201	L4
L3	L2 and articular cartilage	9033	L3
L2	L1 and cartilage regeneration	45708	L2
L1	5972368.pn.	1	L1

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L18: Entry 1 of 1 File: USPT Feb 3, 1998

DOCUMENT-IDENTIFIER: US 5713374 A
TITLE: Fixation method for the attachment of wound repair materials to cartilage defects

US Patent No. (1):
5713374

Brief Summary Text (6):
Techniques were developed to utilize autologous tissue, such as transplantation of: 1) osteochondral grafts (DePalma, et al. 1963); 2) chondrocytes (Grande, et al. 1989); 3) periosteum (Homminga, et al., 1990); and 4) demineralized bone (Dahlberg and Kreicbers, 1991). These techniques have been used to transplant whole or partial joints, with mixed results. For example, a number of investigators attempted to heal cartilage defects using chondrocytes isolated from epiphysial plates, as well as articular cells, with the hypothesis that these cells would have a greater chance of success due to their heightened metabolism (Itay, et al. 1987). Clinical studies using cultured cells reported excellent results, showing a significant decrease in pain and restoration of normal function after two to four years post-op (Iloika, et al. 1990; Ilomminga, et al. 1990).

Brief Summary Text (7):
Other investigators have used a combination of materials and autologous tissue to effectively repair cartilage defects, such as: 1) demineralized bone with perichondrium (Billing, et al., 1990) 2) polylactic acid matrices and periosteal graft (von Schroeder, et al. 1991); and 3) bioresorbable meshes and chondrocytes (Freed, et al. 1993). Although these approaches gave repair tissue that more closely resembled normal cartilage than either the unfilled sites, or the sites filled with materials alone, it was evident that there was again a substantial amount of fibrocartilage formation.

Other Reference Publication (2):
Amiel, Coutts, Harwood, Ishiuze, and Kleiner: The Chondrogenesis of Rib Periochondrial Grafts for Repair of Full Thickenss Articular Cartilage Defects in a Rabbit Model, Connective Tissue Research 18:27-39 (1988).

Other Reference Publication (5):
Convery, Akeson, Keown; The Repair of Large Osteochondral Defects, Clinical Orthopedics and Related Research 82:253-262 (1972).

Other Reference Publication (14):
von Schroder, Kwan, Amiel and Coutts: The Use of Polylactic Acid Matrix and Periosteal Grafts for the Reconstruction of Rabbit Knee Articular Defects. Journal of Biomedical Materials Research 25:329-339 (1991).

Other Reference Publication (15):
Vachon, McIlwraith, Powers, McFadden and D.Amiel: Morphologic and Biochemical Study of Sternal Cartilage Autographs for Resurfacing Induced Osteochondral Defects in Horses. American Journal of Veterinary Research 53:1039-1047 (1992).

Other Reference Publication (17):
Homminga, Bulstra, Kuijer and Anton J. van der Linden: Repair of sheep articular

cartilage defects with a rabbit costal perichondrial graft. Department of Orthopedics, University Hospital Masstricht, The Netherlands.

graft to resorb inside the cage. Subsidence, or sinking of the device into bone, may also occur when metal implants are implanted between vertebrae if fusion is delayed. Metal devices are also foreign bodies which can never be fully incorporated into the fusion mass.

Brief Summary Text (12):
Various bone grafts and bone graft substitutes have also been used to promote osteogenesis and to avoid the disadvantages of metal implants. Autograft is often preferred because it is osteoinductive. Both allograft and autograft are biological materials which are replaced over time with the patient's own bone, via the process of creeping substitution. Over time a bone graft virtually disappears unlike a metal implant which persists long after its useful life. Stress shielding is avoided because bone grafts have a similar modulus of elasticity as the surrounding bone. Commonly used implant materials have stiffness values far in excess of both cortical and cancellous' bone. Titanium alloy has a stiffness value of 114 Gpa and 316L stainless steel has a stiffness of 193 Gpa. Cortical bone, on the other hand, has a stiffness value of about 17 Gpa. Moreover, bone as an implant also allows excellent postoperative imaging because it does not cause scattering like metallic implants on CT or MRI imaging.

Brief Summary Text (13):
Various implants have been constructed from bone or graft substitute materials to fill the intervertebral space after the removal of the disc. For example, the Cloward dowel is a circular graft made by drilling an allogeneic or autogeneic plug from the illium. Cloward dowels are bicortical, having porous cancellous bone between two cortical surfaces. Such dowels have relatively poor biomechanical properties, in particular a low compressive strength. Therefore, the Cloward dowel is not suitable as an intervertebral spacer without internal fixation due to the risk of collapsing prior to fusion under the intense cyclic loads of the spine.

Brief Summary Text (15):
Unfortunately, the use of bone grafts presents several disadvantages. Autograft is available in only limited quantities. The additional surgery also increases the risk of infection and blood loss and may reduce structural integrity at the donor site. Furthermore, some patients complain that the graft harvesting surgery causes more short-term and long-term pain than the fusion surgery.

Brief Summary Text (17):
Both allograft and autograft present additional difficulties. Graft alone may not provide the stability required to withstand spinal loads. Internal fixation can address this problem but presents its own disadvantages such as the need for more complex surgery as well as the disadvantages of metal fixation devices. Also, the surgeon is often required to repeatedly trim the graft material to obtain the correct size to fill and stabilize the disc space. This trial and error approach increases the length of time required for surgery. Furthermore, the graft material usually has a smooth surface which does not provide a good friction fit between the adjacent vertebrae. Slippage of the graft may cause neural and vascular injury, as well as collapse of the disc space. Even where slippage does not occur, micromotion at the graft/fusion-site interface may disrupt the healing process that is required for fusion.

Brief Summary Text (18):
Several attempts have been made to develop a bone graft substitute which avoids the disadvantages of metal implants and bone grafts while capturing advantages of both. For example Unilab, Inc. markets various spinal implants composed of hydroxyapatite and bovine collagen. In each case developing an implant having the biomechanical properties of metal and the biological properties of bone without the disadvantages of either has been extremely difficult or impossible.

Brief Summary Text (19):
These disadvantages have led to the investigation of bioactive substances that regulate the complex cascade of cellular events of bone repair. Such substances include bone morphogenetic proteins, for use as alternative or adjunctive graft materials. Bone morphogenetic proteins (BMPs), a class of osteoinductive factors from bone matrix, are capable of inducing bone formation when implanted in a

fracture or surgical bone site. Recombinantly produced human bone morphogenetic protein-2 (rhBMP-2) has been demonstrated in several animal models to be effective in regenerating bone in skeletal defects. The use of such proteins has led to a need for appropriate carriers and fusion spacer designs.

Brief Summary Text (20):
Due to the need for safer bone graft materials, bone graft substitutes, such as bioceramics, have recently received considerable attention. The challenge has been to develop a bone graft substitute which avoids the disadvantages of metal implants and bone grafts while capturing the advantages of both. Calcium phosphate ceramics are biocompatible and do not present the infectious or immunological concerns of allograft materials. Ceramics may be prepared in any quantity which is a great advantage over autograft bone graft material. Furthermore, bioceramics are osteoconductive, stimulating osteogenesis in boney sites. Bioceramics provide a porous matrix which further encourages new bone growth. Unfortunately, ceramic implants typically lack the strength to support high spinal loads and therefore require separate fixation before the fusion.

Brief Summary Text (25):
A need has also remained for bone graft substitutes which provide the osteogenic potential and low risk of infectious or immunogenic complications of autograft without the disadvantages of autograft.

Brief Summary Text (27):
In accordance with one aspect of the invention, bone graft compositions and vertebral spacers composed of bone graft compositions are provided. In one aspect, the invention provides deactivated bone graft compositions in synergistic combination with a bone growth factor.

Brief Summary Text (28):
One object of the invention is to provide a bone graft substitute having the natural mineral structure, nonimmunogenicity, safety and osteoinductive potential of autograft. Another object of the invention is to provide spacers for engagement between vertebrae which restore the intervertebral disc space and supports the vertebral column while encouraging bone ingrowth and avoiding stress shielding.

Brief Summary Text (29):
One benefit of the present invention is that it solves many of the problems associated with the use of bone graft. The deactivation process removes immunogenic and disease causing agents while retaining the natural micro-structure of bone. This feature allows the use of xenograft, which is available in virtually unlimited supply. Fortifying the graft with a bone growth factor makes the graft osteoinductive which makes the pain and risk of harvesting autograft unnecessary. An additional benefit is that the invention provides a stable scaffold for bone ingrowth before fusion occurs. Still another benefit of this invention is that it allows the use of bone grafts without the need for metal cages or internal fixation, due to the increased speed of fusion. Other objects and further benefits of the present invention will become apparent to persons of ordinary skill in the art from the following written description and accompanying Figures.

Drawing Description Text (13):
The present invention provides bone graft substitute compositions, spacers and surgical procedures. The bone graft compositions include selectively deactivated bone grafts in synergistic combination with an osteogenic material, such as a bone morphogenic protein (BMP). The bone grafts are selectively deactivated to remove all of the cellular material, fat and non-collagenous protein. In preferred embodiments, free collagen is also removed leaving structural or bound collagen which is associated with bone mineral to form the trabecular struts of bone. Although the graft is deproteinated and defatted, it still contains the natural crystalline structure of bone. Therefore, the deactivated bone of this invention has the natural micro-structure of bone without the risk of disease transmission or significant immunogenicity.

Drawing Description Text (15):
When the selectively deactivated bone materials of this invention are combined with

an osteogenic factor such as bone morphogenetic protein, the composite is an ideal bone graft substitute. The composite has the natural calcium phosphate structure of bone. This facilitates incorporation and substitution of the graft material giving the composites a desirable resorption rate of a few months. This compares favorably to the resorption rates of known materials which are typically either too fast, slow or unpredictable. For example, allograft typically is resorbed within 12-60 months but may, on the other hand, resorb too quickly before fusion can occur due to an immunogegenic response by the patient.

Drawing Description Text (16):
The combination of BMP and other osteogenic factors with a selectively deactivated bone graft according to this invention provides the osteoinductive potential of autograft without the need for a harvesting surgery. The osteoinductive composites of this invention enhance bone growth into and incorporation of the graft, resulting in fusion quicker than with graft alone. Allograft alone typically requires many months to incorporate and sometimes is never fully incorporated, but is merely encased within the patient's bone. The quicker fusion occuring within about five months provided by this invention compensates for the less desirable biomechanical properties of graft and makes the use of internal fixation and metal interbody fusion devices unnecessary. The spacers of this invention are not required to support the cyclic loads of the spine for very long because of the quick fusion rates which reduce the biomechanical demands on the spacer. However, when required the compositions of this invention may be used with internal fixation devices or may be reinforced as disclosed in copending U.S. Pat. application Ser. No. 08/872,689, filed on Jun. 11, 1997.

Drawing Description Text (17):
A further advantage provided by this invention is that because the bone is selectively deactivated, the graft may be autogeneic, allogeneic or xenogeneic. The components of bone which could cause disease or prompt the patient's body to reject the graft are removed by the deactivation process. Xenogenic bone, such as bovine bone, is available in virtually unlimited supply. Several osteogenic factors are also available in unlimited supply thanks to recombinant DNA technology. Therefore, the present invention solves all of the problems associated with autograft, allograft and xenograft, including supply, immunogeneicity, disease transmission or additional surgeries.

Drawing Description Text (19):
This invention also capitalizes on the discovery that cortical bone, like metal, can be conveniently machined into the various shapes disclosed herein. In some embodiments, the load bearing members define threads on an outer surface. Machined surfaces, such as threads, provide several advantages that were previously only available with metal implants. Threads allow better control of spacer insertion than can be obtained with a smooth surface. This allows the surgeon to more accurately position the spacer which is extremely important around the critical neurological and vascular structures of the spinal column. Threads and the like also provide increased surface area which facilitates the process of bone healing and creeping substitution for replacement of the donor bone material and fusion. These features also increase post-operative stability of the spacer by engaging the adjacent vertebral endplates and anchoring the spacer to prevent expulsion. This is a major advantage over smooth grafts. Surface features also stabilize the bone-spacer interface and reduce micromotion to facilitate incorporation and fusion.

Drawing Description Text (20):
The bone graft substitute compositions of this invention can be prepared according to conventional methods. Bone of human or animal source is obtained according to known procedures. The bone is cleaned to remove tissue and blood and is then treated with agents to remove cellular material, fats and noncollagenous proteins. Typical agents include alcohols and peroxides. In preferred embodiments, the bone material is also treated to remove free collagen, leaving bound or structural collagen. This reduces immunogenicity without compromising the structural integrity of the bone material. One preferred agent for removing free collagen and any remaining fat is sodium dodecyl sulfate (SDS). The deactivated bone material is then preferably washed with deionized water and sterilized by suitable methods.

Drawing Description Text (23):
The bone materials of this invention are preferably synergistically combined with an osteogenic composition or material containing a bone growth factor or protein. An osteogenic material can be applied to the bone material by impregnating the graft with a solution including an osteogenic composition. The allograft is allowed to soak for sufficient enough time to allow the allograft to absorb the protein. Additional protein could be used with the allograft by the incorporation of the protein of a delivery vehicle and placed around or in the allograft. In some embodiments, an osteogenic composition can be packed into a chamber defined within a body of the material. The composition may be applied by the surgeon during surgery or the spacer may be supplied with the composition preapplied. In such cases, the osteogenic composition may be stabilized for transport and storage such as by freeze-drying. The stabilized composition can be rehydrated and/or reactivated with a sterile fluid such as saline or water or with body fluids applied before or after implantation. The term osteogenic composition used here means virtually any material that promotes bone growth or healing including natural, synthetic and recombinant proteins, hormones and the like.

Drawing Description Text (25):
The choice of carrier material for the osteogenic composition is based on the application desired, biocompatibility, biodegradability, and interface properties. The bone growth inducing composition can be introduced into the pores of the bone material in any suitable manner. For example, the composition may be injected into the pores of the graft. In other embodiments, the composition is dripped onto the graft or the graft is soaked in or sprayed with a solution containing an effective amount of the composition to stimulate osteoinduction. In either case the pores are exposed to the composition for a period of time sufficient to allow the liquid to throughly soak the graft. The osteogenic factor, preferably a BMP, may be provided in freeze-dried form and reconstituted in a pharmaceutically acceptable liquid or gel carrier such as sterile water, physiological saline or any other suitable carrier. The carrier may be any suitable medium capable of delivering the proteins to the spacer. Preferably the medium is supplemented with a buffer solution as is known in the art. In one specific embodiment of the invention, rhBMP-2 is suspended or admixed in a carrier, such as water, saline, liquid collagen or injectable bicalcium phosphate. In a most preferred embodiment, BMP is applied to the pores of the graft and then lypholized or freeze-dried. The graft-BMP composition can then be frozen for storage and transport Alternatively, the osteoinductive protein can be added at the time of surgery.

Drawing Description Text (29):
The present invention also provides spacers for maintaining a space between adjacent bones. The spacers include a body composed of a selectively deactivated bone graft in synergistic combination with a bone growth factor. The bone source is any suitable bone material preferably of any vertebrae origin, including tibial, fibial, humeral, iliac, etc. The bodies of this invention include flat spacers, bone dowels, cortical rings, bone chips and any other suitably shaped bone piece. A preferred body is obtained from the diaphysis of a long bone having a medullary canal which forms a natural chamber in the graft.

Drawing Description Text (32):
In another embodiment depicted in FIG. 3, the body is a bone dowel 20 which includes a wall 22 having an engagement surface 23. The wall 22 defines a chamber 25 therethrough. Preferably, the load bearing member is a bone graft obtained from the diaphysis of a long bone having a medullary canal which forms the chamber 25. Such dowels are available from the UFTB. The chamber 25 can be packed with an osteogenic composition to stimulate osteoinduction. The chamber 25 is preferably defined through a pair of outer engaging surfaces 23 so that the composition has maximum contact with the endplates of the adjacent vertebrae. Referring now to FIG. 4, the spacer 20 preferably includes a solid protective wall 26 which is positionable to protect tbe spinal cord from escape or leakage of material packed within the chamber 25. In anterior approaches, the protective wall 26 is posterior. Preferably, the osteogenic composition has a length which is greater than the length of the chamber (FIGS. 5 and 6) and the composition is disposed within the chamber 25 to contact the end plates of adjacent vertebrae when the spacer 20' is implanted between the vertebrae. This provides better contact of the composition with the end plates to

stimulate osteoinduction.

Drawing Description Text (35):
The body may also include other shapes such as cortical rings as shown in FIG. 7. Such cortical rings 50 are obtained by a cross-sectional slice of the diaphysis of a long bone and include superior surface 51 and inferior surface 52. The graft shown in FIG. 7 includes an outer surface 53 which is adjacent and between the superior 51 and inferior 52 surfaces. In one embodiment bone growth thru-holes 53a are defined through the outer surface 53 to facilitate fusion. The holes 53a allows mesenchymal stem cells to creep in and bone growth protein to diffuse out of the graft. This facilitates bone graft incorporation and possibly accelerates fusion by forming anterior and lateral bone bridging outside and through the device. In another embodiment the outer surface 53 defines a tool engaging hole 54 for receiving an implanting tool. In a preferred embodiment, at least one of the superior and/or inferior surfaces 51,52 are roughened for gripping the end plates of the adjacent vertebrae. The surface roughenings may include teeth 56 on ring 50' as shown in FIG. 8 or waffle pattern 57 as shown on ring 50" in FIG. 9. When cortical rings are used as the graft material the ring 50 may be trimmed for a more uniform geometry as shown in FIG. 7 or left in place as shown in FIG. 9.

Drawing Description Text (36):
The graft can also be formed into a square shape to be conveniently incorporated into current surgical procedures such as, the Smith-Robinson technique for cervical fusion (Smith, M. D., G. W. and R. A. Robinson, M. D., "The Treatment of Certain Cervical-Spine Disorders By Anterior Removal Of The Intervertebral Disc And Interbody Fusion", J. Bone And Joint Surgery, 40-A:607-624 (1958) and Cloward, M. D., R. B., "The Anterior Approach For Removal Of Ruptured Cervical Disks", in meeting of the Harvey Cushing Society, Washington, D.C., Apr. 22, 1958). In such procedures, the surgeon prepares the endplates of the adjacent vertebral bodies to accept a graft after the disc has been removed. The endplates are generally prepared to be parallel surfaces with a high speed burr. The surgeon then typically sculpts the graft to fit tightly between the bone surfaces so that the graft is held by compression between the vertebral bodies. The bone graft is intended to provide structural support and promote bone ingrowth to achieve a solid fusion of the affected joint. The spacers of this invention avoid the need for this graft sculpting as spacers of known size and dimensions are provided. This invention also avoids the need for a donor surgery because the osteoinductive properties of autograft are not required. The spacers can be combined with osteoinductive materials that make allograft osteoinductive. Therefore, the spacers of this invention speed the patient's recovery by reducing surgical time, avoiding a painful donor surgery and inducing quicker fusion.

Detailed Description Text (5):
A dowel was obtained as a transverse plug from the diaphysis of a long bone using a diamond tipped cutting bit which was water cleaned and cooled. The bit was commercially available (Starlite, Inc) and had a generally circular nature and an internal vacant diameter between about 10 mm to about 20 mm. The machine for obtention of endo- and cortical dowels consisted of a pneumatic driven miniature lathe which is fabricated from stainless steel and anodized aluminum. It has a spring loaded carriage which travels parallel to the cutter. The carriage rides on two runners which are 1.0 inch stainless rods and has a travel distance of approximately 8.0 inches. One runner has set pin holes on the running rod which will stop the carriage from moving when the set pin is placed into the desired hole. The carriage is moveable from side to side with a knob which has graduations in metric and in English. This allows the graft to be positioned. On this carriage is a vice which clamps the graft and holds it in place while the dowel is being cut. The vice has a cut out area in the jaws to allow clearance for the cutter. The lathe has a drive system which is a pneumatic motor with a valve controller which allows a desired RPM to be set.

Detailed Description Text (6):
First, the carriage is manually pulled back and locked in place with a set pin. Second, the graft is loaded into the vice and is aligned with the cutter. Third, the machine is started and the RPM is set, by using a knob on the valve control. Fourth, the set pin, which allows the graft to be loaded onto the cutter to cut the dowel.

Once the cutter has cut all the way through the graft the carriage will stop on a set pin. Fifth, sterile water is used to eject dowel out of the cutter. It is fully autoclavable and has a stainless steel vice and/or clamping fixture to hold grafts for cutting dowels. The graft can be positioned to within 0.001" of an inch which creates dowel uniformity during the cutting process.

Detailed Description Text (7):
The cutter used in conjunction with the above machine can produce dowels ranging from 5 mm to 30 mm diameters and the sizes of the cutters are 10.6 mm; 11.0 mm; 12.0 mm; 13.0 mm; 14.0 mm; 16.0 mm; and 18.0 mm. The composition of the cutters is stainless steel with a diamond powder cutting surface which produces a very smooth surface on the wall of the dowels. In addition, sterile water is used to cool and remove debris from graft and/or dowel as the dowel is being cut (hydro infusion). The water travels down through the center of the cutter to irrigate as well as clean the dowel under pressure. In addition, the water aides in ejecting the dowel from the cutter.

Detailed Description Text (14):
Allograft was procured using standard accepted practices according to Example 1. Under clean room conditions, the graft was cut up into desired final physical shape and size, into cylindrical cortical bone dowels. The allograft was then chemically treated to enzymatically dissolve and remove all cellular and non-collagenous proteinaceous material to reduce immunogenicity and risk of disease transmission. The graft was soaked in isopropyl alcohol to dissolve fat. The graft was then soaked in peroxide to remove non-collagenous proteins and fat. The deproteinated and defatted graft was then exposed to SDS to remove free collagen and any remaining fat, leaving structural collagen. The deactivated graft was then washed with deionized water to rinse processing chemicals and debris. Gamma irradiation terminal sterilization was then employed. The resulting allograft primarily consisted of structural collagen and natural bone mineral.

Detailed Description Text (32):
4. The allograft bone dowel is allowed to soak in the rhBMP-2 solution for 30-60 minutes so that the graft absorbs the protein.

Detailed Description Text (82):
The combination of a bone growth factor with a deactivated bone graft provides superior results. Quicker fusion rates provide enhanced mechanical strength sooner. The deactivated bone of this invention is an excellent protein carrier which provides controlled release of BMP to the fusion site. The presence of structural collagen and the natural mineral structure of bone results in an elasticity and radiopacity which is identical or nearly identical to bone. The material has sufficient resilience and elasticity to retain a formed body and yet remains rigid enough to maintain an open space between bone portions to result in a fusion mass.

CLAIMS:

1. A bone graft substitute composition, comprising:

natural selectively deactivated bone material which has been processed to remove associated non-collagenous bone proteins, said bone material containing native collagen materials and naturally associated bone minerals and substantially free from native non-collagenous protein; and

a therapeutically effective amount to stimulate bone growth of a bone growth factor in a pharmaceutically acceptable carrier dispersed within said bone material.

2. The bone graft substitute of claim 1 wherein said deactivated bone is processed at temperatures no higher than about 250.degree. C.

3. The bone graft substitute of claim 1 wherein said deactivated bone is substantially free from free collagen.

4. The bone graft substitute of claim 1 wherein said bone growth factor is recombinant BMP-2.

5. The bone graft substitute of claim 2 wherein said bone growth factor is recombinant BMP-2.

14. The spacer of claim 6 wherein said bone graft is bovine bone.